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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/529,053
Filing Date: April 06, 2000
Appellant(s): WILLIAMS ET AL.

Michael F. Borun
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed June 22, 2004.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The brief contain a statement indicating that there are no pending appeals or interference related to the present application.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that claims 16,17,19-25; and claims 18 do not stand or fall together based on Weithmann and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8). The brief also includes a statement that claims 16-25 will stand or fall together based on Coghlan.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

The following is a listing of the prior art of record relied upon in the rejection of claims under appeal.

US Patent 5,556,870	Weithmann et al.	September 17, 1996
WO 94/24095	Coghlan et al.	October 27, 1994

McChesney et al. 'An evaluation of leflunomide in the canine renal transplantation model,' Transplantations, 1994, vol. 57, No. 12, pages 1717-1722.

Flamand et al. 'Human herpes virus 6 induces interluekin-1β and tumour necrosis factor alpha, but not interleukin-6, in peripheral blood mononuclear cell cultures,' Journal of virology,' 1991, vol. 65, No. 9. pages 5105-5110.

Hammer 'Advances in antiretroviral therapy and viral load monitoring,' AIDS, 1996, (suppl 3) pages s1-s11.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 16, 17 and 19-25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) and in further view of Flamand et al. and Hammer with respect to claims 19, 22 and 23.

2. Claims 16-25 are rejected under 35 U.S.C. 103(a) over Coghlan et al. (WO 94/24095) in view of McChesney et al. in further view of Hammer with respect to claims 22 and 23.

These rejections are fully set forth in prior office action, mailed September 23, 2003, but are reiterated in full below

(11) Response to Argument

The appealed claims are directed to method of treating, or prophylactically treating, virual infections with leflunomide products. The limitation "for inhibiting viral replication in cells," recited in the claims was not given patentable weight as discussed in the following.

3. Claims 16, 17, 20, 21, 24, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870).

4. Weithmann et al. teach a method of treating disorder in which interleukin 1 beta is involved (produced). The disorders include viral infections, such as HIV or hepatitis, comprising administering leflunomide to the patient. See, particularly, the abstract and the claim. The dosage may range from 3-50 mg daily, but may be higher if required. See, particularly, column 3, lines 7-16.

1. Weithmann et al. does not teach expressly the amount effective to inhibit viral virion assembly. However, the optimization of a result effective parameter, e.g., effective amount for a therapeutical dosage of a known therapeutical agent, is considered within the skill of the artisan. See, In re Boesch and Slaney (CCPA) 204 USPQ 215. Further, treating a disease with an agent in a host would lead the agent contacting the pathogenic cell. A method known to be useful for treating viral infection would have been reasonably expected to be useful for prophylactic purpose. Further, known anti-viral agents would have been reasonably expected to be effective in vitro against virus. Finally, since leflunomide is effective against viruses through different mechanism than viral DNA replication, it would have been reasonably expected to be effective against those viruses with resistance to antiviral agent that inhibit viral DNA replication. As to the limitation "for inhibiting viral replication in cells," note the functional limitation of the method is not seen to make the otherwise obvious method patentably distinct. It is noted that the

effective amount herein is within the range of effective amounts disclosed by Weithmann et al. (see col. 3, lines 6-16 in Weithmann et al. and page 16, lines 17-29 in the specification herein).

Claim 19 is rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Flamand et al.

Claim 19 is obvious for reasons discussed above and in further view of Flamand et al. Weithmann et al. do not teach expressly the method for treating herpes.

5. However, Flamand et al. teaches that herpes infection is involved with interleukin 1 beta. (promote the product of interleukin 1 beta) See, particularly, the abstract.

6. Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the method of Weithmann for treating herpes infections.

7. A person of ordinary skill in the art would have been motivated to employ the method of Weithmann for treating herpes infections, because herpes infection is known to be involved interleukin 1 beta. (promote the production of interleukin 1 beta).

8. Claims 22, and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Weithmann et al. (US Patent 5,556,870) in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11).

9. Claims 22 and 23 are obvious over Weithmann et al. as discussed above, and further in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11).

Weithmann et al. do not teach expressly the employment of addition antiviral agent in the method.

10. However, Hammer teaches that several pyrimidine compounds are known antiviral agents. See, particularly, page s3.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds with other antiviral agents such as those known pyrimidine compounds Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; thus , the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

Claims 16-20, 21, 24, 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coghlan et al. (WO 94/24095) in view of McChesney et al. (Transplantation, Vol. 57, no. 12, page 1717-1722).

11. Coghlan et al. teaches compounds with general structures that encompass leflunomide or its active metabolite, the compounds have similar biological activity to leflunomide or its metabolite. See, particularly, the abstract, page 2, the examples and the claims. The expressly taught compounds includes those meet the leflunomide products (page 18-19 in the specification). Compounds closely related to leflunomide have been expressly disclosed (see, particularly, the claims). These compounds are known to be useful for treating or preventing

viral infection such as hepatitis and cytomegalovirus infection, particularly, HCMV. See, page 4, lines 23-32.

12. Coghlan et al. does not teach expressly the employment leflunomide or its metabolite, or the particular amount herein for treating viral infections.

13. However, McChesney et al. teaches that both leflunomide and A771726 are known to be effective in preventing viral infection. See, particularly, the abstract at page 1717, and the materials and method at page 1717-1718.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis and CMV.

2. A person of ordinary skill in the art would have been motivated to employ the compounds taught by Coghlan et al., including both leflunomide and A771726, for treating or prevention viral infections such as hepatitis and CMV because these compounds are known to be useful for treating or preventing viral infection, and both leflunomide and A771726 are known to be similarly useful as the other compounds. Finally, since leflunomide is effective against virus through different mechanism than viral DNA replication, one would have reasonably expected it to be effective against those viruses resistant to antiviral agent that inhibit viral DNA replication. As to the limitation "for inhibiting viral replication in cells," note the functional limitation of the method is not seen to make the otherwise obvious method patentable distinct.

Claims 22 and 23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Coghlan et al. (WO 94/24095) in view of McChesney et al. (Transplantation, Vol. 57, no. 12, page 1717-1722), and further in view of Hammer (AIDS 1996, vol. 10, suppl 3, s1-s11).

Coghlan et al. (WO 94/24095), and McChesney et al. do not teach expressly the employment of an additional antiviral agent in the method.

14. However, Hammer teaches that several pyrimidine compounds are known antiviral agents. See, particularly, page s3.

Therefore, it would have been prima facie obvious to a person of ordinary skill in the art, at the time the claimed the invention was made, to employ a combination of leflunomide compounds with other antiviral agents such as known pyrimidine compounds Also, it is prima facie obvious to combine two compositions each of which is taught in the prior art to be useful for same purpose in order to form a third composition that is to be used for very the same purpose; idea of combining them flows logically from their having been individually taught in prior art; Thus, the claimed invention which employ a combination of two known anti-viral agents sets forth prima facie obvious subject matter. See In re Kerkhoven, 205 USPQ 1069. Further, combination therapies for viral infection are known to be better than single agent therapy. See, Hammer, page s2, the paragraph of combination therapy.

Response to the Arguments

15. Appellants argue there is no prima facie case of obviousness in view of Weithmann because that Weithmann et al. lack credibility with respect to treating viral infection claimed therein (see also the 132 declaration by Wadman filed June 26, 2003). The arguments have been fully considered, but are not persuasive. Particularly, Weithmann specifically claims a method of

treating HIV infection, hepatitis with a leflunomide products. Further, Since every patent is presumed valid (35 U.S.C. 282), and since that presumption includes the presumption of operability (Metropolitan Eng. Co. v. Coe, 78 F.2d 199, 25 USPQ 216 (D.C.Cir. 1935), examiners should not express any opinion on the operability of a patent. Affidavits or declarations attacking the operability of a patent cited as a reference must rebut the presumption of operability by a preponderance of the evidence. In re Sasse, 629 F.2d 675, 207 USPQ 107 (CCPA 1980). (See, also, MPEP 716.07).

3. Appellants further argue the claimed invention is not obvious over Weithmann et al. since appellant shows in vitro and in vivo examples of leflunomide products effectively inhibiting viral replication, and Weithmann et al. lack such data. The arguments are not convincing. Note the claims are construed as treating patient with viral infection, or susceptible to viral infection. Weithmann et al. particularly teach that method. The instant claims are directed to effecting a biochemical pathway with old and well known compounds. The argument that such claims are not directed to the old and well known ultimate utility (treating viral infection) for the compounds, e.g., leflunomide, are not probative. It is well settled patent law that mode of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Appellant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered function or property, inherently possessed by a thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." In the instant invention, the claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical intermediates. The ultimate utility for the claimed compounds is old and well known rendering

the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

4. Appellants argue that there is not prima facie obviousness of claim 19 based on Weithmann in view of Flamand because Flamand provide no suggestion or motivation that any therapeutical agent capable of inhibiting the production of IL-1β would also be capable of inhibiting virus replication in the infected patient. The examiner agrees that Flamand provide no suggestion or motivation that any therapeutical agent capable of inhibiting the production of IL-1β would also be capable of inhibiting virus replication in the infected patient. However, that is not the necessary condition to provide motivation. Weithmann et al. teach a method of treating disorders in which interleukin 1 beta is involved, HIV and hepatitis are particularly mentioned, with interleukin-1 beta. Weithmann et al. explains the treatment are based on inhibting the synthesis of interleukin-1 beta. See. Column 1, line 50 to column 2, line 8. Weithmann et al. do not expressly teach treating herpes viral infection. However, Flamand teaches that herpes viral infection also involves IL-1β production. One of ordinary skill in the art would have reasonable expected that the method of Weithmann et al be similarly useful for treating herpes viral infection.

5. Appellants further argue that there is no prima facie case of obviousness of claims 22 and 23 based on Weithmann in view of Hammer. Specifically, appellants assert that leflunomide products are not known as anti-viral agents and therefore there is no motivation to combine. The examiner disagrees. One of ordinary skill in the art would consider any agent that provides benefit for a patient with viral infection as antiviral agent. Since both agents, i.e., leflunomide

products and the other anti-viral agents are known to be useful for treating viral infection, idea of combining them flows logically from their having been individually taught in prior art.

In response to appellants' argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "a pyrimidine" is not an antiviral agent) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Note "pyrimidine" herein includes compounds useful either directly, or as *intermediates* in pathway for supplying pyrimidine nucleotides (pages 20 of the specification herein). The antiviral compound disclosed by Hammer certainly met the limitation.

6. Appellants allege that Coghlan, or McChesney does not teach the isoxazole compounds structurally related to leflunomide products inhibit viral replication, and therefore, the claimed invention is not obvious over Coghlan, and McChesney. These arguments have been fuly considerd, but are not persuasive. The examiner agrees that Coghlan, or McChesney does not teach that the isoxazole compounds structurally related to leflunomide products inhibit viral replication. However, the claimed method which reads on treating patient infected with HIV, hepatitis, or herpes is obvious over Coghlan, or McChesney. As stated above, with respect to the limitation "for inhibiting viral replication in cells," note the functional limitation of the method is not seen to make the otherwise obvious method patentable distinct. The instant claims are directed to effecting a biochemical pathway with an old and well known compound. The argument that such claims are not directed to the old and well known ultimate utility (antiviral) for the compounds, e.g., leflunomide, is not probative. It is well settled patent law that the mode

of action elucidation does not impart patentable moment to otherwise old and obvious subject matter. Applicant's attention is directed to In re Swinehart, (169 USPQ 226 at 229) where the Court of Customs and Patent Appeals stated "is elementary that the mere recitation of a newly discovered functionary property, inherently possessed by thing in the prior art, does not cause a claim drawn to those things to distinguish over the prior art." The claims are directed to the ultimate utility set forth in the prior art, albeit distanced by various biochemical intermediates. The ultimate utility for the claimed compounds is old and well known rendering the claimed subject matter obvious to the skilled artisan. It would follow therefore that the instant claims are properly rejected under 35 USC 103.

In response to appellants' arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). Particularly, Coghlan et al. teaches the usefulness of leflunomide products for treating viral infection. McChesney et al. discloses that leflunomide, or its metabolite, is effective to prevent viral infection. McChesney is cited to show further evidence that using leflunomide for prophylactic purpose is obvious. Therefore, take the cited reference as a whole, using leflunomide for treating and prophylactic treating viral invention would have been obvious.

Appellants further argue that there is no prima facie obviousness of claims 22 and 23 based on Coghlan, in view of McChesney, in further view of Hammer. Particularly, appellant asserts Coghlan et al. does not teach leflunomide products as anti-viral agents and therefore there is no motivation to combine. The examiner disagree. One of ordinary skill in the art would

consider any agent that provide benefit for patient with viral infection as an antiviral agent. Since both agents, i.e., leflunomide products and the other anti-viral agents are known to be useful for treating viral infection, idea of combining them flows logically from their having been individually taught in prior art.

In response to appellants' argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., "a pyrimidine" is not an antiviral agent) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). Note "pyrimidine" herein includes compounds useful either directly, or as *intermediates* in pathway for supplying pyrimidine nucleotides (pages 20 of the specification herein). The antiviral compound disclosed by Hammer certainly met the limitation.

Appellants further argue even if there is a prima facie case, it has been rebutted by objective evidence, citing 132 declaration by Wadman and the data cited therein. As discussed above, the newly discovered function herein, i.e., inhibiting viral replication, does not render any material difference in treating viral infection by leflunomide. Such function fails to distinguish the claimed method from the old and well-known method.

16. Appellants also contend that the prima facie case over Coghlan in view of McChesney has been rebutted, citing the declaration of Mocarski. The examiner disagrees. As discussed in the prior office action, the declaration by Edward s. Mocarski under 37 CFR 1.132 filed June 26, 2003 is insufficient to overcome the rejection of claims 16-25 based upon Coghlan et al. in view of McChesney et al. as set forth above: The rejections are based on the conbined cited references,

not on McChesney. The examiner agrees that McChesney does not teach or suggest *conclusively* that leflunomide is antiviral active. However, McChesney at least suggests that leflunomide is useful in preventing viral infection. In view the totality of cited references, the claims are obvious as discussed above.

17. Further, appellants erred in asserting that the isoxazole compounds disclosed by Coghlan et al. are "structurally distinct from leflunomide products" herein. As stated above, Coghlan et al. teaches compounds with general structures that encompass leflunomide or its active metabolite, the compounds have similar biological activity of leflunomide or its metabolite. See, particularly, the abstract, page 2, the examples and the claims. For example, with respect to formula 1 (acyl isoxazole, the E therein may be $NR^{14}R^{15}$, wherein R^{14} and $R^{15}$are independently hydrogen or aryl groups, and wherein the aryl may be substituted by halo, halosubstitued alkyl. See, particularly, page 5 and page 24, or the claims. Further, the compounds disclosed by Coghlan et al. are analogues, or derivatives of leflunomide and are expected to be similarly useful as leflunomide as immunomodulating agents. See, page 2 in Coghlan.

For the above reasons, it is believed that the rejections should be sustained.

SHENGJUN WANG
PRIMARY EXAMINER

Respectfully submitted,

Shengjun Wang
Primary Examiner
Art Unit 1617

September 7, 2004

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